EDUCATIONAL ATTAINMENT AND RATE OF COGNITIVE DECLINE IN ALZHEIMER'S DISEASE

A Dissertation

by

LAURA SUE HEMMY

Submitted to the Office of Graduate Studies of
Texas A&M University
in partial fulfillment of the requirements for the degree of

DOCTOR OF PHILOSOPHY

December 2006

Major Subject: Psychology

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Approved by:

Chair of Committee,	Douglas K. Snyder
Committee Members,	Robert W. Heffer
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ABSTRACT

Educational Attainment and Rate of Cognitive Decline

in Alzheimer's Disease. (December 2006)

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Alzheimer's disease (AD) progression and hypotheses of the cognitive reserve theory were investigated by testing for a relation between educational attainment and rate of decline in patients with Mild Cognitive Impairment, possible AD, probable AD, and other progressive neurodegenerative dementias. Patient data (n = 726) were acquired from a clinical database at the Minneapolis VAMC GRECC Memory Loss Clinic. Analyses using mixed effect regression models found education was significantly related to an accelerated rate of decline in global cognition (MMSE: -0.022, SE = 0.007, p = .003) and a steeper linear rate of decline in functional ability (Cognitive Performance Test: -0.034, SE = 0.011, p = .005). Cox proportional hazard models found little evidence to support an association between educational attainment and relative mortality risk. These results are consistent with previous findings and predictions of the cognitive reserve theory.

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INTRODUCTION

Alzheimer's disease (AD) is by far the most common of the degenerative dementias, with incidence and prevalence rates increasing with advancing age (Fratiglioni, De Ronchi, & Aguero-Torres, 1999) and estimated projections predicting the prevalence will quadruple by the year 2050 (Brookmeyer & Gray, 2000). A long preclinical phase of AD exists in which one does not yet meet criteria for the diagnosis of dementia, further increasing the number of individuals in the population at any one time affected by the disease. In this preclinical phase, neuropathological changes are already present and cognition has started to decline, but without overtly noticeable symptoms of any kind. Some have estimated the pre-clinical phase of AD, in which cognition is slowly declining but one does not yet meet criteria for dementia, can last 10 years or more (Elias et al., 2000; La Rue & Jarvik, 1987). Memory loss is most frequently the first overt sign of the disease which will eventually progress to include globally impaired cognition and an inability to perform activities of daily living and care for one's self.

There is great variability in the course of decline both between patients and within one individual's experience of the disease at different times (Galasko, Corey-Bloom, & Thal, 1991; Han, Cole, Bellavance, McCusker, & Primeau, 2000; Storandt, Grant, Miller, & Morris, 2002; Teri, McCurry, Edland, Kukull, & Larson, 1995). A considerable amount of research has been dedicated to explaining this variability, yet few predictors of decline have produced consistent results. For example, a recent meta-

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This dissertation follows the style of *Neuropsychology*.

analysis including data from 37 studies (total sample size = 3492) tracking cognitive decline in AD failed to find any population characteristic that accounted for a significant proportion of variance in the rate of decline (Han et al., 2000).

Cognitive decline in normal aging

Cross-sectionally, it is generally accepted that more education is associated with better cognitive test performance at any age, and this effect has also been demonstrated with older adults (Bäckman, Small, Wahlin, & Larsson, 1999; Fillenbaum, Hughes, Heyman, George, & Blazer, 1988; Folstein, Folstein, & McHugh, 1975; Scherr et al., 1988; Snowdon, Ostwald, Kane, & Keenan, 1989). In a qualitative review of the literature, education was also found to be one of few predictors to have a consistent effect on rate of cognitive decline in late adulthood (Anstey & Christensen, 2000). The majority of studies evaluating this effect have found those with higher educational attainment show less cognitive decline with advancing age (Albert et al., 1995; Christensen et al., 1997; Colsher & Wallace, 1991; Evans et al., 1993; Farmer, Kittner, Rae, Bartko, & Regier, 1995; Leibovici, Ritchie, Ledesert, & Touchon, 1996; Reynolds, Gatz, & Pedersen, 2002). There is some evidence to suggest the association of education and rate of decline may be limited to abilities with a high learned component such as verbal or crystallized abilities (Anstey & Christensen, 2000; Christensen et al., 1997; Leibovici et al., 1996) and one study found the effect to be greater in women (Colsher & Wallace, 1991).

There are several possible explanations for the association of higher levels of education with less cognitive decline in old age. The more highly educated may: (a) be

at less risk of central nervous system damage from illness, injury, dietary deficiency, or alcoholism (presumably from lifestyle factors and more availability of resources), (b) have greater neuronal reserve capacity or reduced risk of damage (either acquired or innate), (c) have greater ability to compensate for the effects of aging, or (d) be better able to perform on structured cognitive evaluations (assessment bias) despite their true cognitive abilities. These explanations will be addressed in a later section.

Incidence and prevalence of Alzheimer's disease

Greater educational attainment has also been associated with a decreased incidence and prevalence of AD. The results of several large epidemiological studies from different cultural settings support this conclusion (Gatz et al., 2001; Y. Stern et al., 1994; Tognoni et al., 2005; Zhang et al., 1990). In addition, two studies found limited evidence to support higher education as a protective factor against the diagnosis of AD or dementia. In one the effect was limited to one of two cognitive measures with a small effect size and minimal clinical significance (Galasko, Gould, Abramson, & Salmon, 2000), and in the other it was limited to white participants only (Fitzpatrick et al., 2004). A few studies have failed to find a significant relation between education and the incidence or prevalence of AD (Elias et al., 2000; Fratiglioni et al., 1991; Kawas, Gray, Brookmeyer, Fozard, & Zonderman, 2000). In one there was a trend for fewer years of education to be associated with higher incidence of AD, but is was not statically significant (Kawas et al., 2000). Another found less education to be associated with higher dementia prevalence, but not specifically in AD (Fratiglioni et al., 1991). Finally, one study failed to find any association between education and the occurrence of AD,

although it was restricted to a sample of mostly white, well educated participants (Beard, Kokmen, Offord, & Kurland, 1992).

Interestingly, two studies have reported higher education is associated with a *younger* age of dementia onset. One was a retrospective study restricted to a sample of identified Alzheimer's patients, as opposed to a prospective incidence study (Chui, Lyness, Sobel, & Schneider, 1994). The other found the effect in a heterogeneous sample of patients diagnosed with a variety of dementia types (Del Ser, Hachinski, Merskey, & Munoz, 1999).

Rate of decline in Alzheimer's disease

A variety of studies have found educational attainment is related to rate of cognitive decline in AD, but not always in what may be the expected direction based upon the findings reviewed above. As might be expected, two studies have found higher education to be associated with a slower rate of cognitive decline in AD (Drachman, O'Donnell, Lew, & Swearer, 1990; Fritsch, McClendon, Smyth, & Ogrocki, 2002). However, in one of these studies lower education was also associated with poorer performance on baseline measures of functioning and the effect was no longer significant once disease severity was included in the predictive model (Drachman et al., 1990). Somewhat counterintuitive at first glance, a considerable amount of evidence suggests an accelerated rate of cognitive decline in AD for those with *higher* levels of formal education (Gould, Abramson, Galasko, & Salmon, 2001; Rasmusson, Carson, Brookmeyer, Kawas, & Brandt, 1996; Teri et al., 1995; Wilson et al., 2004). Two additional studies found similar trends but the effect was not as robust. In the first, a

more rapid decline on memory tests was evident in patients with higher educational attainment, but was only statically significant for those patients with lower initial cognitive functioning at baseline (Stern, Albert, Tang, & Tsai, 1999). Using data from the CERAD program, the second study also found more education was associated with accelerated decline in AD, with only marginally significant results (Mendiondo, Ashford, Kryscio, & Schmitt, 2000).

Several studies have failed to find any relation between education and cognitive decline in AD (Bäckman, Jones, Small, Aguero-Torres, & Fratiglioni, 2003; Burns, Jacoby, & Levy, 1991; Butters, Lopez, & Becker, 1996; Chui et al., 1994; Doody, Massman, & Dunn, 2001; Storandt et al., 2002; Suh, Ju, Yeon, & Shah, 2004). A meta-analysis of studies evaluating rate of decline in AD using the MMSE, found such great heterogeneity in the rate of decline across studies that none of the patient characteristics modeled accounted for a statistically significant proportion of the variance in rate of decline (Han et al., 2000). Similarly, a qualitative review of studies following change over time in AD concluded that the variability in rate of cognitive change and prognosis in AD has not been adequately explained (Galasko et al., 1991). Most studies of decline in AD last between one and three years and it is often suggested longer follow-up periods are needed to observe any consistent moderators of rate of decline (Galasko et al., 1991; Nyenhuis & Garron, 1997; Wilson et al., 2004).

Finally, progression of AD can be measured by rate of change on continuous measures such cognitive tests or functional assessments, or by the attainment of clinical endpoints such as nursing home placement or death. These varied outcome measures

may not necessarily have the same predictors. The majority of studies have reported that educational attainment is not significantly related to survival rate in AD (Butters et al., 1996; Heyman, Peterson, Fillenbaum, & Pieper, 1996; Storandt et al., 2002), although one study did find patients with more education had an increased mortality rate (Stern, Tang, Denaro, & Mayeux, 1995).

In summary, there is general consensus that higher education appears to be protective against cognitive decline in aging, possibly due to prevention, delayed onset or the ability to mask decline in observable performance. There is also support for the argument that more education is associated with a reduced risk of being diagnosed with AD (maybe dementia in general), although these results are less consistent. Finally, there is no consensus as of yet that education is consistently related to rate of cognitive decline in AD. When such an effect has been found, those with more education usually exhibit an accelerated rate of decline.

What might be responsible for the relation between education attainment and cognitive status in late life? Why would more education be predictive of better functioning in "normal" old age and also related to a steeper rate of decline in AD? Few have suggested that education itself causes better health, and a variety of possible mechanisms have been proposed to account for the relation between education and cognitive status and why the effect may appear to reverse direction after the diagnosis of a neurodegenerative disease such as AD.

Education as a biased predictor

As reviewed earlier, there is a consistent positive relation between education and cross-sectional performance on cognitive tests. This effect may be only partially due to constructs such as intelligence or other "innate" abilities. Those who are better educated may also simply be better at taking structured tests. The process of education itself may allow for better performance on tests used to measure cognitive abilities, and those with more education (and hypothetically equivalent innate ability) would be expected to perform better when tested than persons with less education. It has also been suggested that age may be confounded with educational attainment in today's cohort of older adults (Elias et al., 2000). This might especially be the case in those groups most likely to have either been in school during the depression or possible beneficiaries of the G.I. bill after World War II.

However, there is some evidence to suggest that the relation between education and dementia prevalence and incidence cannot be completely accounted for by an education-related bias in age or cognitive testing. In one study, lower educational attainment was associated with an increased prevalence of dementia even when the dementia diagnosis was based on functional ability scales alone (Hill et al., 1993). Another study (Y. Stern et al., 1994) attempted to address possible assessment bias issues by re-analyzing their data to account for several possible sources of bias including: (a) test reliability (by eliminating subjects who had been close to the dementia cutoff at first assessment and would be more likely to be perceived as declining to dementia status at time two simply as a result of small testing variation), (b)

bias due to the relation between cognitive test performance and education (re-classified dementia cases using functional testing alone), and (c) cohort effects (split participants into separate samples of age cohorts). None of these procedures changed the result that the more highly educated were less likely to develop dementia.

There is also reason to believe that the association of education and delayed dementia onset may be specific to AD, which would further argue against incidence and prevalence rates as simply reflective of an education and cognitive decline main effect. The Swedish Twin study found low education to be a risk for AD, but not dementia in general (Gatz et al., 2001). Similarly, an Italian epidemiological study found low education status increased the risk of Mild Cognitive Impairment (MCI) and AD, but not of vascular dementia or dementia in general (Tognoni et al., 2005). The same investigators that re-analyzed their data for assessment bias, also did so restricting their data to cases of pure AD (Y. Stern et al., 1994). Again, their results (that the more highly educated were less likely to develop dementia) remained the same and produced the strongest effect yet. The authors argue that such an outcome would not be expected if test bias or a cognition-education main effect were the primary source of variance (as opposed to pathology); such biases would be expected to distribute equally across pathology groups. Finally, a study of probable AD patients and normal older adult controls found that although education was significantly related to several measures of cognitive decline (especially language measures), an interaction was present in which education played a greater role in test performance among the AD patients than among the controls (Becker, Huff, Nebes, Holland, & Boller, 1988). However, it should be

noted the patient and control subjects were not matched on age and education which would have removed potential sources of bias and made for a stronger argument.

Education as a proxy indictor for other patient characteristics

Education may be a surrogate that co-varies with a variety of innate ability and life experience variables such as intelligence, occupation, recreational activities, income, illness, diet/nutrition, exposure to environmental toxins and pollutants, access to medical care, or personal health habits (e.g., responsibility for health behaviors, alcohol intake, or smoking). Of these variables, occupation has received the most attention. Several studies failed to find any unique effect of occupation (above that accounted for by education) on the rate of decline in AD (Beard et al., 1992; Fritsch et al., 2002; Stern, Tang et al., 1995). One study found an interaction between education and occupation such that the risk of dementia was highest for those individuals with both low education and low occupational attainment, suggesting a synergistic effect of the two variables (Y. Stern et al., 1994). Composite socioeconomic status estimates have been associated with higher levels of cognitive ability in late life, but not with incident risk or rate of decline in AD (Beard et al., 1992; Wilson et al., 2005). Finally, the Swedish Twin study found lower levels of self-reported "intellectual involvement" earlier in life for those twins who later became demented (Gatz et al., 2001) and similarly, the risk of dementia has been reported as decreased in subjects with high demand leisure activities (Scarmeas, Levy, Tang, Manly, & Stern, 2001).

Protective vs. compensatory process

Aside from the discussion of whether "education effects" are really produced by the experience of education itself (as opposed to other correlated person or lifestyle characteristics), the relatively consistent relation between education and preserved cognitive ability prior to the onset of clinical AD may indicate the presence of either protective or compensatory processes. A protective process would indicate that the effect of education or its hypothesized important covariates somehow prevent decline (for example by slowing biological aging) in the more highly educated. A compensatory process fails to alter the normal course of decline with age (or pathology), but adjusts to these changing circumstances in a manner that allows for preserved performance (and delayed clinical symptoms). For example, some have investigated specific examples of neural compensation in older adults, defining the concept as the use of an altered network that would not usually be used in younger or disease free individuals (Stern et al., 2005). The authors emphasize that a compensatory process does not require evidence of improved performance, but simply maintenance of performance in the context of aging or disease pathology.

Reserve hypothesis

Similar to the concept of compensation, a reserve hypothesis has been proposed to account for the seemingly disparate effects of education on cognitive decline (delayed impairment in normal aging, delayed diagnosis of AD and increased rate of decline in identified AD patients). Stern and colleagues (2005) have defined two types of reserve. The first, cognitive reserve, describes individual differences in mental *processing* that

provide differential reserve against brain pathology or age-related changes (e.g., brain networks that are more efficient or flexible may be less susceptible to disruption). The second, neural reserve refers to normally occurring variability in the *capacity* to perform tasks or cope with increases in task difficulty. Reserve in any one individual may come from a variety of sources, including innate characteristics and life experiences. Stern and colleagues make a distinction between reserve, a back-up resource called in times of external challenge (Stern et al., 2005), and compensation, an altered strategy aimed at preserving ability in the face of internal disruption (Stern et al., 2000).

How does this concept of reserve account for the relation found between education and cognitive decline described above? The reserve hypothesis proposes that individual difference and life experience variables provide increased reserve capacity that allows individuals to cope with the effects of AD pathology for a longer time before showing clinical symptoms of the disease. In this way education may help to preserve cognitive performance and delay the diagnosis of AD (reducing incidence rates).

However, the progression of disease pathology has not been altered. Once those with higher levels of education have been diagnosed with AD (and, by definition, clinical symptoms have become evident), they have expended their reserve and would be expected to decline at a steeper rate due to the higher pathology burden in the brain. Several studies have supported this hypothesis by demonstrating the underlying neuropathology of AD is more advanced in those with higher levels of education, despite an equivalent level of outwardly observable symptoms such as cognitive or functional ability (Bennett, Schneider, Wilson, Bienias, & Arnold, 2005; Scarmeas et al., 2003;

Stern, Alexander, Prohovnik, & Mayeux, 1992; Stern, Tang et al., 1995). The majority of these studies estimate disease severity using regional cerebral blood flow (rCBF). However, one study followed participants to autopsy and was able to show that for those with higher education a significantly weaker relation existed between amyloid burden and cognition (Bennett et al., 2005). The interaction was not found for neurofibrillary tangles.

Some have attempted to replicate these results with correlates of education that might also be responsible for a reserve effect. Indicators of more advanced AD (measured by rCBF and time to death, after controlling for education and disease severity) have been found in those with more demanding occupations (Stern, Alexander et al., 1995; Stern, Tang et al., 1995). In addition, one study found evidence that more advanced AD (measured with rCBF) was uniquely related to higher education, National Adult Reading Test (NART)-estimated IQ scores, and greater activity engagement (a composite score including intellectual, social, and physical activities), each while controlling for age, dementia severity, and the other predictors of interest (Scarmeas et al., 2003).

Study objectives

This study contributes to the literature on disease progression and cognitive reserve by testing for an association between educational attainment and rate of global cognitive decline and functional decline in patients with AD spectrum diagnoses and other neurodegenerative dementias. Despite a wealth of research, the nature of the relation between formal education and rate of decline in AD is still not well understood.

Although it appears higher levels of education may lead to an increased rate of decline in clinical AD, this finding has not been consistent. Several mechanisms have been proposed to explain the association, and of them, the reserve hypothesis seems the most promising (given the replicated finding that those with higher levels of education show more advanced disease pathology). Therefore, it is hypothesized that (1) higher levels of formal education will be significantly related to an accelerated rate of global cognitive decline in AD, and (2) the shape of the overall progression in AD is curvilinear. Survival analyses will also evaluate the mortality hazard associated with educational attainment relative to baseline cognitive ability and functional ability alone.

METHOD

Participants

Study participants were part of an ongoing clinical database at the Geriatric Research, Education and Clinical Center (GRECC) Memory Loss Clinic at the Minneapolis, MN Veterans Affairs Medical Center (VAMC) that draws from a community-dwelling population of older adults. Patient data were included in the study if (1) the patient had a diagnosis of Mild Cognitive Impairment (MCI; Petersen, 2004), Possible or Probable Alzheimer's disease according to NINCDS-ADRDA criteria (McKhann et al., 1984), or other progressive neurodegenerative dementia at his or her most recent clinic visit, (2) had been seen in the GRECC Memory Loss Clinic and administered either the Mini-Mental State Exam (MMSE) on a minimum of three occasions or the Cognitive Performance Test (CPT) on a minimum of two occasions, and (3) had the following demographic information available: age at initial clinic visit, gender, and years of education. A total of 726 individuals were identified that met the above criteria, including 80 with a diagnosis of MCI, 80 with possible AD, 464 with probable AD, and 102 with other neurodegenerative dementias[1].

Procedure

This study utilized retrospective data. No active recruitment, intervention or assessment was conducted. All data collection was conducted as part of a Human Studies IRB approved clinical database at the GRECC at the Minneapolis VAMC. The

[1] Other neurodegenerative dementias were included as a comparison group that does not lie solely within the AD spectrum but is still expected to decline. In the present study this included the following: mixed dementia (n = 27), dementia with Lewy bodies (n = 19), fontal lobe and fronto-temporal dementias (n = 30), multiple system atrophy (n = 2), Parkinson's disease (n = 21), primary progressive aphasia (n = 1) and progressive supranuclear palsy (n = 2).

present study received approval from the above institution to retrieve de-identified patient data from this ongoing clinical database.

Measures

Mini-Mental State Exam. Cognitive decline was assessed using the Mini-Mental State Exam (MMSE; Folstein et al., 1975), a measure with both advantages and disadvantages in characterizing change in Alzheimer's patients. An advantage of using the MMSE is that it is by far the most widely used screening instrument in the assessment of dementia. The vast majority of published research on cognitive decline in Alzheimer's disease reports MMSE scores. Although popularity itself does not confer any particular advantage, the use of the MMSE allows for direct comparison with results from an extensive body of literature. The MMSE has been shown to have good test-retest reliability in Alzheimer's patients (ranging from .74 to .94), as well as moderate-to-high correlations with other cognitive screening instruments and measures of disease progression (see Tombaugh & McIntyre, 1992 for review).

One disadvantage of using the MMSE is a flattening of the slope at the very beginning and end of the disease due to floor and ceiling effects in some samples, since the MMSE is most sensitive to cognitive decline in moderate dementia (Tombaugh & McIntyre, 1992). However, the present sample consists mostly of patients with moderate impairment[2] which should minimize potential floor and/or ceiling effects. Additionally, the MMSE is not ideal for the measurement of very mild differences over time and the validity of any measured change on the MMSE improves with longer

[2] Mean initial MMSEs in the present study range from 19.79 to 26.47 depending on the analysis and diagnostic group.

observation intervals (Clark et al., 1999; van Belle, Uhlmann, Hughes, & Larson, 1990). For this reason, analyses using the MMSE were restricted to those participants with a minimum of three observation points. Finally, performance on the MMSE has been shown to be related to educational attainment in older adults, and education often accounts for more variance in the MMSE score than other demographic variables such as gender or race (see Tombaugh & McIntyre, 1992, for review). However, considerable disagreement exists as to whether this effect is independent or represents the direct effect of educational attainment as a risk factor for cognitive decline.

Cognitive Performance Test. The Cognitive Performance Test (CPT; Burns, Mortimer, & Merchak, 1994) is a performance-based functional ability measure based on the Allen Cognitive Disability theory (Allen & Allen, 1987). The CPT has been shown to have good inter-rater and test-retest reliability (.91 and .89, respectively) and is correlated with other instruments measuring functional ability and activities of daily living (Burns et al., 1994). The main advantages of the CPT are its coverage of both activities of daily living (ADLs) and instrumental activities of daily living (IADLs) and its performance-based administration (avoiding potential biases introduced by caregiver or other informant ratings).

Data analysis

Rate of decline. The associations between education and rate of decline on the MMSE and CPT were examined using mixed effects (also known as hierarchical or multilevel) linear and quadratic regression models (Singer & Willett, 2003). Mixed effects models have several advantages over traditional repeated measures approaches

for modeling change over time, including: allowance for missing data and varying measurement of time intervals across participants, are fairly robust to violations of various statistical assumptions, they do not require completely normally distributed variables, and allow for dummy-coded or nominal predictors (Fritsch et al., 2002).

The mixed effects model is a two-stage (hierarchical) restricted maximum likelihood analysis approach. The first stage produces a best estimate of an individual participant's initial score (MMSE or CPT) and slope of decline (based upon all available scores for that participant), the best linear unbiased predictor (BLUPS). This method is preferred over subtraction or least squares estimates, providing greater power for detecting differences and minimizing floor and ceiling effects when compared with the above other choices (Galasko et al., 2000; Gould et al., 2001). In stage two, the first stage estimates are used to describe variability across participants and the effect of predictor variables (i.e. age, years of education). The mixed effects models approach to evaluating change over time has been cited as the preferred method for tracking decline in Alzheimer's disease (Gould et al., 2001; Rasmusson et al., 1996; Reynolds et al., 2002).

In the present study, the age and education variables entered into the mixed models were centered on the whole number values closest to the average values for the entire sample. Thus, age was centered at 75 years-old and education was centered at 12 years. This procedure produces more meaningful intercept values that correspond to an individual who is 75 years of age and has 12 years of formal education (as opposed to an estimated intercept for one with 0 years of age and 0 years of education). Each set of

analyses (MMSE and CPT) began by testing an unconditional growth model and then successive models individually added age, education, gender, and interaction effects. Non-significant terms were dropped from carrying on to future models with the exception of age and education which were included as covariates in all models.

Some evidence suggests that the natural course of decline in AD is likely non-linear (Morris et al., 1993; R. G. Stern et al., 1994; Storandt et al., 2002; Teri et al., 1995). However, the majority of studies have either assumed a linear rate of decline or were restricted to one due to less than three assessment points or a particular method of analysis (Clark et al., 1999; Gould et al., 2001; Han et al., 2000; Rasmusson et al., 1996; Suh et al., 2004). Analyses tested for a linear annual rate of change on the MMSE and CPT to facilitate comparison with previously published studies, as well as for a non-linear rate of change over time on the MMSE (where a minimum of three data points were available).

Survival analyses. Cox regression (also known as Cox proportional hazard) models were used to assess the effect of initial assessment score (MMSE or CPT) and education on the relative risk of death. Cox models allow for in the inclusion of covariates in non-discrete time-to-event data and have important advantages over alternative hazard estimation methods (see Singer & Willett, 2003 for a detailed discussion). No assumption is made about the shape of the baseline hazard function and the method is robust to variation, and even error, in the measurement of time (so long as the rank order of events among participants is not disturbed). In the present analyses, each set of models (one for the MMSE and one for the CPT) began by testing for the

effects age and initial assessment score alone, and successive models added gender, education and interaction terms.

RESULTS

Demographic data

Study participants (n = 726) were seen in the GRECC Memory Loss Clinic between November 1988 and July 2006. They had an average age of 75.68 (SD = 6.84) years at initial assessment, were 97% male, and had an average of 12.19 (SD = 3.23) years of education. A total of 559 individuals were identified with three or more MMSE assessment points and were included in the mixed model analyses separated by diagnostic group (MCI, possible AD, probable AD, and other degenerative dementias). The average interval between initial and most recent MMSE evaluation was 2.23 (SD = 1.81) years and participants were seen for an average of 4.33 (SD = 2.38) assessment occasions. Two additional sets of mixed model analyses were ran on sub-samples of this group, restricting to those with a diagnosis of probable AD and a minimum of either four (n = 260) or five (n = 176) MMSE assessment points. These probable AD sub-groups with a minimum of four and five assessment points had average intervals between initial and most recent MMSEs of 3.23 (SD = 1.81) and 3.81 (SD = 1.79) years and an average total number of 5.93 (SD = 2.19) and 6.85 (SD = 2.11) assessment points (respectively).

Eighty-six individuals were identified with a minimum of 2 CPT assessment points. However, too few fell in the diagnostic categories of MCI (n = 8), possible AD (n = 7), and other neurodegenerative dementias (n = 6) to be included in the analyses.

Thus, only individuals with a diagnosis of probable AD and a minimum of 2 CPT assessment points (n = 65) were included in the mixed model analyses for the CPT. Their average interval between initial and most recent CPT evaluation was 1.75 (SD = 1.10) years and they were seen for an average of 2.22 (SD = 0.52) assessment points.

Because the Cox regression models do not require multiple follow-up data points, a greater number of those initially identified to participate were included in these analyses. A total of 644 individuals (divided by diagnostic group) were included in those models assessing the effect of initial MMSE score and education on mortality risk, and 359 were included in those models assessing the effect of initial CPT score and education on mortality risk. This excluded those with a diagnosis of MCI, due to an inadequate number of deaths (5.0% with the MMSE and 6.8% with the CPT) in those groups to run the analyses. Complete demographic information for all analysis sets and diagnostic groups are presented below in Table 1.

Table 1
Participant Demographic Characteristics by Diagnostic Group

		Age at initial evaluation		Years of education		Initial MMSE/CPT		Male gender
Diagnostic group	n	M	SD	M	SD	M	SD	%
Mixed models with 3+ MMSE data points								
MCI	53	73.95	7.30	13.36	3.16	26.47	2.48	98.1
Possible AD	62	75.29	7.70	11.66	3.18	23.29	4.27	98.4
Probable AD	367	76.27	5.90	12.00	3.22	20.31	5.18	95.6
Other dementias	77	72.61	7.95	11.91	3.24	21.94	4.84	100.0
Total	559	75.43	6.68	12.08	3.23	21.45	5.20	96.8
Mixed models with 4+ MMSE data points								
Probable AD	260	75.98	5.98	12.00	3.10	20.75	4.83	95.4
Mixed models with 5+ MMSE data points								
Probable AD	176	75.50	6.15	12.10	3.18	21.15	4.64	93.8
Mixed models with 2+ CPT data points								
Probable AD	65	75.68	6.30	12.28	2.84	4.67	0.40	100.0
Cox regression models with MMSE								
Possible AD	80	74.80	7.67	11.75	3.14	23.35	4.20	97.5
Probable AD	462	76.76	6.03	12.12	3.20	19.79	5.52	95.2
Other dementias	102	73.13	7.65	11.92	3.40	21.63	5.27	100.0
Total	644	75.71	6.81	12.19	3.23	21.18	5.54	96.6
Cox regression models with CPT								
Possible AD	39	74.73	7.59	11.90	3.34	4.92	0.38	97.4
Probable AD	272	77.56	5.60	12.31	3.06	4.66	0.41	96.0
Other dementias	48	73.31	8.71	11.69	3.43	4.59	0.51	100.0
Total	359	76.68	6.51	12.18	3.14	4.68	0.43	96.7

Note. AD = Alzheimer's disease; CPT = Cognitive Performance Test; MMSE = Mini-Mental State Exam

Rate of decline (mixed effects models)

MMSE. Unconditional growth models were fit for each diagnostic group. Estimates of initial visit MMSE scores were 26.50 (SE = 0.28, p = .000) for the MCI group, 23.52 (SE = 0.51, p = .000) for the possible AD group, 20.64 (SE = 0.27, p = .000) for the probable AD group, and 21.92 (SE = 0.57, p = .000) for the other

degenerative dementias group. Only the MCI group failed to produce a significant annual rate of change on the MMSE (0.06, SE = 0.09, p = .573). For the remaining groups estimated annual rates of *decline* (in MMSE points) were as follows: 1.17 (SE = 0.26, p = .000) for possible AD, 2.02 (SE = 0.12, p = .000) for probable AD and 2.01 (SD = 0.26, p = .000) for the other degenerative dementias group. Age at time of initial MMSE assessment was then added to each of the models, but did not have a significant effect on the initial MMSE score for any of the four diagnostic groups (MCI: 0.00, SE = 0.03, p = .945; possible AD: 0.04, SE = 0.07, p = .596; probable AD: 0.01, SE = 0.05, p = .802; other degenerative dementias: -0.04, SE = 0.07, p = .570). Age at intercept nevertheless remains in each succeeding model in to be more comparable with the majority of literature available on rate of decline in AD. The effect of initial age on the slope was tested (time by age interaction) and was also found to be non-significant in all four diagnostic groups (MCI: -0.00, SE = 0.02, p = .895; possible AD: -0.03, SE = 0.03, p = .255; probable AD: -0.02, SE = 0.02, p = .136; other degenerative dementias: -0.04, SE = 0.03, p = .229). Next education was added to each model. Education did have a significant effect on initial MMSE score for the MCI and probable AD groups (MCI: 0.19, SE = 0.06, p = .003; probable AD: 0.49, SE = 0.08, p = .000), but not for the possible AD or other degenerative dementia groups (possible AD: 0.19, SE = 0.17, p = .253; other degenerative dementias: 0.30, SE = 0.17, p = .085). For those in the MCI and probable AD groups, one year of additional education was estimated to produce a 0.19 and 0.49 (respectively) increase in initial MMSE score. Gender was then added to the models for those groups including females (MCI, possible AD and probable AD).

Models were tested adding (1) only the effect of gender on the intercept (initial MMSE) and (2) the effect gender on the slope (time by gender interaction). Neither gender (MCI: 0.58, SE = 1.42, p = .685; possible AD: -3.67, SE = 4.09, p = .372; probable AD: 1.14, SE = 1.29, p = 377) nor the time by gender interaction (MCI: 0.02, SE = 1.15, .987; possible AD: 0.60, SE = 1.77, p = .736; probable AD: 0.33, SE = 0.53, p = .536) were significant for any of the three groups and gender was dropped from all subsequent models. Finally, a time by education interaction term was added to test for the effects of education on slope. This interaction term was only significant for the probable AD diagnostic group (MCI: -0.01, SE = 0.03, p = .809; possible AD: -0.05, SE = 0.08, p = .530; probable AD: -0.08, SE = 0.04, p = .022; other degenerative dementias: 0.00, SE = 0.08, p = .964). For each additional year of education, probable AD patients' MMSE scores declined an additional 0.08 points per year.

Thus far, all models have assumed a linear rate of decline on the MMSE. The next set of models tested for a curvilinear rate of decline by adding a quadratic term ($time^2$). Models for two of the groups (MCI and other degenerative dementias) failed to converge, possibly due to small sample sizes (n = 53 and 77, respectively), and the estimates for the quadratic component was not significant for either group (MCI: -0.09, SE = 0.07, p = .207; other degenerative dementias: -0.03, SE = 0.06, p = .999). The quadratic component estimate was also non-significant for the possible AD group (-0.05, SE = 0.05, p = .408), indicating that a linear slope is a better fit for this group. However, the quadratic component estimate was significant for the probable AD group (-0.14, SE = 0.04, p = .000), indicating a curvilinear rate of decline on the MMSE for this group.

Patients with probable AD were declining at an additional rate of 0.14 MMSE points each year beyond the rate of the previous year.

In order to test the hypothesis that higher educational attainment is associated with not just a steeper rate of decline, but a progressively accelerating rate of decline, a time^2 by education interaction term was added to the model. Because there was no prior evidence to suggest a curvilinear slope in the other groups, this hypothesis was tested with the probable AD group only. Two versions of this model were tested. The first included education interaction terms for both the linear (time by education) and curvilinear (time^2 by education) slopes (in addition to the main effects of age and education on the intercept) and the second included only the curvilinear interaction. Both models estimated a significant curvilinear interaction with education (time^2 by education). Because the linear slope interaction (time by education) in the first version was not significant (-0.00, SE = 0.05, p = .972), it was dropped from the model. Patients with probable AD were not only declining at an accelerating rate, but the rate of acceleration was itself increasing by an additional 0.02 (SE = 0.01, p = .003) MMSE points for each additional year of education. Table 2 presents a comparison of those models ran with the probable AD diagnostic group in order as they have been described above.

Table 2
Mixed Model Estimates: Rate of MMSE Decline in Probable AD

	Intercept			Slope			
	MMSE	Age	Educ	Time	T*Educ	Time ^{2}	T^2*Educ
Model A	20.637			-2.019			
	0.272			0.115			
	.000			.000			
Model B	20.622	0.012		-2.030			
	0.279	0.046		0.125			
	.000	.802		.000			
Model C	20.581	0.050	0.489	-2.085			
	0.267	0.045	0.082	0.125			
	.000	.267	.000	.000			
Model D	20.578	0.050	0.476	-2.078	-0.083		
	0.267	0.045	0.082	0.124	0.036		
	.000	.265	.000	.000	.022		
Model E	20.302	0.064	0.467	-1.573		-0.142	
	0.264	0.044	0.081	0.180		0.037	
	.000	.146	.000	.000		.000	
Model G	20.306	0.064	0.442	-1.593	-0.002	-0.132	-0.022
	0.264	0.044	0.081	0.178	0.053	0.035	0.010
	.000	.145	.000	.000	.972	.000	.040
Model F	20.306	0.064	0.442	-1.592		-0.132	-0.022
	0.264	0.044	0.081	0.177		0.035	0.007
	.000	.145	.000	.000		.000	.003

Note. Fixed effect estimates are presented along with standard errors and p values for each variable entered into the model. (AD = Alzheimer's disease; Educ = education; MMSE = Mini-Mental State Exam; T = time variable)

To confirm the findings that (1) patients with probable AD are experiencing an accelerated rate of decline on the MMSE over time (curvilinear slope) and (2) higher education in these patients is associated with an even greater rate of accelerated decline

(time^2 by education interaction), the same models were tested with two subgroups of the patients with probable AD: those with a minimum of four MMSE assessment points, and those with a minimum of five MMSE assessment points. Both groups demonstrated a significant curvilinear rate of decline (4+ data points: -0.18, SE = 0.04, p = .000; 5+ data points: -0.18, SE = 0.04, p = .000). As with the prior set of analyses using those individuals with three or more MMSE assessments, the education interaction was tested with two models: one that included education interaction terms for both the linear (time by education) and curvilinear (time^2 by education) slopes (in addition to the main effects of age and education on the intercept), and one that included only the curvilinear interaction. Both groups failed to show a significant linear time by education interaction (4+ data points: -0.01, SE = 0.06, p = .891; 5+ data points: 0.03, SE = 0.06, p = .608), and it was dropped from the models. Once again, patients with probable AD were not only declining at an accelerating rate, but the rate of acceleration was also increasing with higher levels of education (4+ data points: -0.02, SE = 0.01, p = .004; 5+ data points: 0.02, SE = 0.01, p = .006). Table 3 presents a comparison of those models ran with the two probable AD diagnostic groups restricted to those with a minimum of four and five MMSE assessment points (again, in order as they have been described above).

Table 3

Mixed Model Estimates: Rate of MMSE Decline in Probable AD with a Minimum of 4 and 5 Assessment Points

	Intercept			Slope			
	MMSE	Age	Educ	Time	T*Educ	Time ^{2}	T^2*Educ
Mixed models with 4+ MMSE data points							
Model A	20.824	0.046	0.547	-1.317		-0.176	
	0.281	0.046	0.090	0.190		0.038	
	.000	.327	.000	.000		.000	
Model B	20.831	0.045	0.514	-1.343	-0.008	-0.162	-0.022
	0.281	0.046	0.091	0.188	0.058	0.036	0.011
	.000	.334	.000	.000	.891	.000	.052
Model C	20.831	0.045	0.513	-1.342		-0.162	-0.023
	0.281	0.046	0.090	0.188		0.036	0.008
	.000	.334	.000	.000		.000	.004
Mixed models with 5+ MMSE data points							
Model A	21.181	0.044	0.547	-1.236		-0.175	
	0.325	0.053	0.102	0.215		0.041	
	.000	.406	.000	.000		.000	
Model B	21.191	0.043	0.507	-1.259	0.033	-0.161	-0.027
	0.324	0.053	0.103	0.214	0.064	0.039	0.012
	.000	.417	.000	.000	.608	.000	.025
Model C	21.190	0.043	0.514	-1.257		-0.161	-0.022
	0.324	0.053	0.103	0.213		0.039	0.008
	.000	.419	.000	.000		.000	.006

Note. Fixed effect estimates are presented along with standard errors and p values for each variable entered into the model. (AD = Alzheimer's disease; Educ = education; MMSE = Mini-Mental State Exam; T = time variable)

In order to investigate the effect of the average interval between observations, two models were run restricting the analyses to those patients with probable AD and three or more MMSE assessment points. The first model included the effects of age and

education on the intercept, the quadratic component to account for a curvilinear rate of decline, and added the average time interval between observations, and this variable's interaction with the slope. The second model also added an interaction term for the curvilinear rate of decline and the average time interval between observations ($time^2$ by average observation interval). The curvilinear interaction with average observation interval was not significant (0.01, SE = 0.09, p = .912). The prior model with only the linear interaction term was used to estimate the effect of average observation interval on initial MMSE and rate of decline. In patients with probable AD, each additional year between observations (on average) was associated with a 4.11 higher initial MMSE score (SE = 0.89, p = .000) and a 1.05 lower rate of annual decline (less steep) on the MMSE (SE = 0.37, p = .006).

CPT. All analyses were restricted to those with a diagnosis of probable AD. No gender effects were tested because all participants in this group are male. The unconditional growth model produced an initial CPT estimate of 4.68 (SE = 0.05, p = .000) and a significant estimated rate of annual *decline* of 0.15 CPT points (SE = 0.03, p = .000). Age at time of initial CPT assessment was then added to the model, and produced a significant effect on the intercept. For each year of older age, estimated initial CPT scores decrease by 0.02 (SE = 0.01, p = .035). A time by age interaction term was the added to the model. Initial age did not have a significant effect on the slope (-0.00, SE = 0.00, p = .945). Age at intercept was carried forward to successive models, but the interaction term was not. Next, education was added to the model. Education had no significant effect on initial CPT score (0.02, SE = 0.02, p = .255).

Adding a time by education interaction term demonstrated that education did have a significant effect on the slope (-0.03, SE = 0.01, p = .005). This last model failed to converge, perhaps due to the limited sample size (n = 65). Estimates are nevertheless presented (see Table 4) so as to compare trends with the prior CPT and MMSE models. For each additional year of education, probable AD patients' CPT scores declined an additional 0.03 points per year.

Table 4
Mixed Model Estimates: Rate of CPT Decline in Probable AD

	Intercept			Slope	
	CPT	Age	Educ	Time	Time*Educ
Model A	4.675			-0.147	
	0.049			0.031	
	.000			.000	
Model B	4.686	-0.017		-0.129	
	0.048	0.008		0.032	
	.000	.035		.000	
Model C	4.679	-0.013	0.021	-0.134	
	0.048	0.008	0.018	0.032	
	.000	.118	.255	.000	
Model D	4.673	-0.013	0.021	-0.110	-0.034
	0.044	.008	0.016	0.033	0.011
	.000	.098	.211	.002	.005

Note. Fixed effect estimates are presented along with standard errors and p values for each variable entered into the model. Model D failed to converge, possible due to the relatively small sample size (n = 65). (AD = Alzheimer's disease; CPT = Cognitive Performance Test; Educ = Education)

Survival analyses (Cox regression models)

Cox regression models were performed separately for the MMSE and CPT in order to maximize the number of available subjects in each diagnostic group (fewer participants were assessed with the CPT than the MMSE). All analyses excluded those with a diagnosis of MCI, due to an inadequate number of deaths during observation (5.0% for the MMSE analyses and 6.8% for the CPT analyses). The percentage of deaths observed in the remaining diagnostic groups for the MMSE and CPT analyses (respectively) are as follows: possible AD, 52.5 and 43.6; probable AD, 51.4 and 44.5; and other degenerative dementias, 60.8 and 58.3.

MMSE. The first set of Cox models tested included initial MMSE score and age as predictors of mortality risk in each diagnostic group. Only initial MMSE score was a significant predictor of risk for the possible AD group (hazard ratio 0.91, 95% CI 0.85-0.97, p = .004). A one-point increase on initial MMSE corresponded to a 9.2 percent decrease in relative risk of death. For the probable AD and other degenerative dementias groups, both initial MMSE (probable AD: 0.93, 95% CI 0.91-0.95, p = .000; other degenerative dementias: 0.91, 95% CI 0.87-0.95, p = .000) and age (probable AD: 1.05, 95% CI 1.02-1.07, p = .000; other degenerative dementias: 1.07, 95% CI 1.03-1.11, p = .001) were significant predictors of risk. A one-point increase on initial MMSE corresponded to a 7.0 and 9.3 percent decrease in relative risk, and a one-year increase in age corresponded to a 4.8 and 6.8 percent increase in relative risk for the probable AD and other degenerative dementia groups (respectively). Gender was then added to the models for the possible and probable AD groups (the other degenerative dementias

group is all male). Once again, only initial MMSE was a significant predictor of mortality risk in the possible AD group and gender was not significant (1.17, 95% CI 0.16-8.72, p = .878). However, gender was a significant predictor of mortality risk in the probable AD group (0.50, 95% CI 0.25-0.98, p = .044) with female gender corresponding to a 50.1% reduction in risk. Next, education was added to each model. Patient education had no significant effect on relative mortality risk in any of the three diagnostic groups (possible AD: 1.03, 95% CI 0.94-1.12, p = .566; probable AD: 1.03, 95% CI 0.99-1.07, p = .156; other degenerative dementias: 0.97, 95% CI 0.90-1.05, p = .504). Finally, a MMSE by education interaction term was added to each model. The interaction between initial MMSE and education also had no significant effect on relative mortality risk in any of the three diagnostic groups (possible AD: 0.99, 95% CI 0.97-1.02, p = .528; probable AD: 0.99, 95% CI 0.99-1.00, p = .061; other degenerative dementias: 1.00, 95% CI 0.99-1.02, p = .810), although the effect was marginal in the probable AD group. Table 5 presents a comparison of those models ran with the probable AD group in order as they have been described above.

Table 5
Cox Models for the MMSE in Probable AD

	MMSE	Age	Gender	Educ	Time*Educ
Model A	0.930	1.048			
	0.910-0.951	1.024-1.072			
	.000	.000			
Model B	0.931	1.048	0.499		
	0.911-0.952	1.025-1.072	0.254-0.982		
	.000	.000	.044		
Model C	0.928	1.052	0.459	1.031	
	0.907-0.949	1.028-1.077	0.232-0.912	0.989-1.074	
	.000	.000	.026	.156	
Model D	1.007	1.053	0.466	1.179	0.993
	0.912-1.102	1.029-1.078	0.235-0.924	1.019-1.365	0.985-1.365
	.875	.000	.029	.027	.061

Note. Cox hazard ratios, 95% confidence intervals, and p values are presented for each variable entered into the model. (AD = Alzheimer's disease; Educ = education; MMSE = Mini-Mental State Exam)

CPT. Again, the first set of models tested included initial CPT score and age as predictors of mortality risk in each diagnostic group. All three diagnostic groups demonstrated a significant effect of initial CPT on mortality risk (possible AD: 0.12, 95% CI 0.03-0.57, p = .008; probable AD: 0.44, 95% CI 0.30-0.66, p = .000; other degenerative dementias: 0.41, 95% CI 0.20-0.84, p = .015). A one-point increase in initial CPT score corresponded to an 88.0 (possible AD), 55.7 (probable AD), and 59.4 (other degenerative dementias) percent decrease in relative risk. Age was not associated with significant additional risk in the possible AD (1.07, 95% CI 0.98-1.17, p = .142) and other degenerative dementias (1.04, 95% CI 0.99-1.09, p = .086) groups. It was,

however, in the probable AD group (1.04, 95% CI 1.01-1.08, p = .019). A one-year increase in age corresponded to a 4.3 percent increase in relative risk. As with the MMSE analyses, gender was then added to the models for the possible and probable AD groups only (the other degenerative dementias group is all male). Gender was not a significant predictor of risk for either group (possible AD: 0.00, 95% CI 0.00-0.00, p = .991; probable AD: 0.37, 95% CI 0.11-1.18, p = .092) and was not carried forward to any additional models. Education was then added to each model. Patient education did have a significant effect on the relative mortality risk for those with possible AD (1.20, 95% CI 1.03-1.40, p = .023). Each additional year of education was associated with a 19.5 percent increase in relative risk of mortality. Education did not confer any additional risk for those with probable AD (1.01, 95% CI 0.95-1.08, p = .790) or other degenerative dementias (0.93, 95% CI 0.82-1.05, p = .227). Finally, a CPT by education interaction term was added to each model. The interaction between initial CPT and education had no significant effect on relative mortality risk in any of the three diagnostic groups (possible AD: 1.16, 95% CI 0.74-1.84, p = .517; probable AD: 1.00, 95% CI 0.86-1.15, p = .952; other degenerative dementias: 0.83, 95% CI 0.63-1.08, p = .168). Table 6 presents a comparison of those models ran with the probable AD group in order as they have been described above.

Table 6
Cox Models for the CPT in Probable AD

	CPT	Age	Gender	Educ	Time*Educ
Model A	0.443	1.043			
	0.295-0.664	1.007-1.080			
	.000	.019			
Model B	0.410	1.044	0.367		
	0.270-0.622	1.008-1.080	0.114-1.176		
	.000	.016	.092		
Model C	0.436	1.043		1.009	
	0.287-0.664	1.007-1.080		0.946-1.076	
	.000	.018		.790	
Model D	0.459	1.043		1.029	0.996
	0.083-2.542	1.006-1.081		0.539-1.963	0.864-1.147
	.373	.021		.931	.952

Note. Cox hazard ratios, 95% confidence intervals, and p values are presented for each variable entered into the model. (AD = Alzheimer's disease; Educ = education; CPT = Cognitive Performance Test)

SUMMARY AND CONCLUSIONS

The primary objective of this study was to contribute to the literature on AD progression and cognitive reserve by testing for an association between educational attainment and rate of decline. The cognitive reserve hypothesis proposes that individuals with more years of formal educational (likely representing a multitude of individual difference and life experience variables) have an increased reserve capacity, allowing them to cope with the effects of AD pathology for a longer time before showing clinical symptoms of the disease (Scarmeas & Stern, 2004; Stern et al., 1999). However, the progression of disease pathology has not been altered; once diagnosed with AD, those with higher educational attainment have expended their reserve capacity and are expected to decline at a steeper rate due to a higher pathology burden in the brain (Bennett et al., 2005; Scarmeas et al., 2003; Stern et al., 1992; Stern, Tang et al., 1995). Therefore, the cognitive reserve hypothesis predicts that more years of education should be associated with a steeper rate of decline in patients with AD. If one is able to observe patients early enough (i.e., before the onset of the clinical syndrome) those with higher educational attainment should appear to have an accelerating rate of decline because the slope for these patients captures both a period of delay in clinical symptoms (flatter slope) and a period of relatively steeper decline once diagnosed. These hypotheses were tested utilizing a longitudinal data set of both global cognitive decline (MMSE) and functional decline (CPT) in a sample of patients with MCI, possible AD, probable AD, and other neurodegenerative dementias.

As expected, all groups with a dementia diagnosis demonstrated a significant rate of decline on the MMSE and patients with probable AD were also significantly declining on the CPT. Although it is not surprising that patients with MCI are not declining at a rate comparable to the demented groups, it is interesting that they demonstrated no decline on the MMSE. This may be a ceiling effect and a more sensitive measure of cognitive ability (or specifically memory) might better track change over time in this group. Age had no significant effect on the rate of MMSE decline in any of the diagnostic groups or on the rate of CPT decline in the probable AD group. Likewise, gender also failed to affect the rate of MMSE decline in any group (CPT analyses only included males). Patient education did have a significant effect on rate of decline in the probable AD group. This was the case for both the MMSE and the CPT, arguing against an education-bias in the MMSE as the sole source of the effect. Consistent with the cognitive reserve theory, higher education was found to be associated with a steeper rate of decline on both outcome measures (after adjusting for the effect on initial assessment). Other diagnostic groups failed to produce the effect. This is not entirely surprising, since those in the MCI group would not be expected to have already expended their reserve capacity, and those in the possible AD and other degenerative dementias groups have additional (possible AD) or alternate pathologies (other degenerative dementias) that would shape their rate of decline. However, it is also possible that the lack of finding is due to the smaller sample sizes in these diagnostic groups.

The present study supports a curvilinear rate of decline on the MMSE in patients with probable AD. Although this was not the case for the remaining diagnostic groups, two of the models failed to converge (again, possibly due to small sample size), leaving the findings less interpretable. Many published studies have not tested for a curvilinear rate of decline in AD, even though there is evidence to support this hypothesis (Morris et al., 1993; R. G. Stern et al., 1994; Storandt et al., 2002; Teri et al., 1995). Most significantly, not only were patients with probable AD declining at an accelerated rate, but the rate of acceleration was found be greater in those with more education. It may be that the normal course of AD is non-linear and the cognitive reserve effect seen in the relation of education and rate of decline (less steep decline prior to diagnosis and steeper decline after diagnosis) is simply amplifying the effect at the bend in the curve.

In order to ensure that those participants with longer between observation periods were not overly influencing the rate of decline and possibly producing a spurious result, the effect of this measurement on rate of decline was evaluated. Average time between observations was not significantly associated with the curvilinear rate of decline. It was however, significantly associated with both initial intercept and linear decline in that those with longer periods of time between observations had higher initial MMSE scores and less decline over time (flatter slope). This effect is unlikely to be contributing to a spurious result supporting the cognitive reserve theory, as it is in the opposite direction. Most likely, patients who appear to be doing relatively well when presenting in clinic (i.e., higher initial MMSE scores and less reported change over time) are not scheduled for as frequent follow-up visits.

Higher initial MMSE and CPT scores were both significantly related to a reduction in mortality risk for all dementia patient groups. After modeling for the effects of initial MMSE score and demographic factors (age and gender), patient education had no significant effect on relative mortality risk in any of the groups. This was also the case for the interaction between education and initial MMSE (although the effect appeared marginal in the probable AD group). Findings were similar in the CPT analyses, however the possible AD group did show a significantly increased risk of mortality (19.5%) with each additional year of education. Although, as a whole these results are not particularly supportive of a cognitive reserve effect on survival rate, the one finding is in the expected direction with additional education corresponding to greater relative risk. Several previous studies have also failed to find this effect (Butters et al., 1996; Heyman et al., 1996; Storandt et al., 2002).

Limitations of the present study include its retrospective design, patient population, small sample size for those with diagnoses other than probable AD, and an inability to test for a curvilinear rate of decline on the CPT. In order to gain a better understanding of the true shape of decline in AD it would be most desirable to prospectively follow initially healthy older adults through the complete course of the disease (pre-clinical, MCI, AD diagnosis and death). Participants in the present study were only identified and followed after having been referred to a memory loss clinic and demonstrating some level of impairment. The results of the present study may generalize to a restricted population due the sample having been drawn from a mostly male veteran population in the upper Midwest region of the U.S. Finally, the small

sample sizes for the non-probable AD groups may have contributed to the lack of convergence in several of the mixed models and possibly less reliable estimates. Although it has been suggested that samples of 30 or more are adequate for general multilevel models (Snijders & Bosker, 1999), other have reported samples of 50 or less can lead to biased group-level estimates (Maas & Hox, 2005). Several predictors were used in the present study which may have overwhelmed a sample size that might otherwise be adequate with fewer terms in the models. Finally, this study was unable to address whether the true rate of functional decline in AD is linear or curvilinear. Too few participants had three or more CPT assessments and analyses had to be limited to assuming a linear slope. Ideally, one would like to be able compare the shape of the change trajectory on the cognitive and functional screening instruments, however this was not possible with the current data.

This study also has several strengths. First, the sample size for the probable AD group is large in comparison with most reported studies of MMSE decline in AD (Han et al., 2000). Second, this is a well-defined group of Alzheimer's patients. The largest diagnostic group was restricted to probable AD (as opposed to also including possible AD) in order to minimize the potential for errors in diagnosis and the contribution of various co-morbid conditions that can affect cognitive decline. The administration of the MMSE is standardized in the Minneapolis GRECC Memory Loss Clinic, and the attending physician staff and referral base have remained largely unchanged over the course of data acquisition. Third, the mixed model approach to longitudinal data is the preferred method for modeling change trajectories (Singer & Willett, 2003) and has been

explicitly cited as such in the context of Alzheimer's research (Galasko et al., 2000; Gould et al., 2001; Rasmusson et al., 1996; Reynolds et al., 2002). Fourth, as reviewed above, the present study also restricted the MMSE analyses to include a minimum of three assessment points in order to model both linear and curvilinear rate of change over time. Fifth, the present study tested rate of decline and cognitive reserve hypotheses with both cognitive and functional data. Finally, both continuous outcomes (mixed model analyses) and risk of reaching a clinically meaningful endpoint (Cox proportional hazards) were investigated.

In summary, this study provides further support for the cognitive reserve theory as exhibited in the relation between educational attainment and rate of decline in AD. Higher levels of education were associated with steeper rates of decline in both global cognitive ability and functional impairment. Patients with probable AD were found to be declining at an accelerated rate on the MMSE and higher levels of education exacerbated this trajectory. Generally, education was not found to be associated with mortality risk. However in when it was, higher education conferred additional risk, as would be predicted by the cognitive reserve theory.

Understanding the natural progression of AD and what variables influence that progression are important for both clinical practice and the promotion of research aimed at arresting or curing the disease. A better understanding of disease progression facilitates early detection in order to identify potential candidates for preventative interventions and it helps in the investigation of new treatment interventions by providing a benchmark against which to compare the efficacy of interventions. The

identification of potentially modifiable factors related to progression rate may be useful in either preventing the development or reducing the clinical expression of the disease. Even without any improved ability to prevent or treat AD, increased knowledge about disease progression can provide benefits on both individual patient and provider-system levels. Alzheimer's patients' and their caregivers' experiences may be improved by knowing what to expect and being able to plan for the anticipated course of the disease. Health care provider systems may be better able to maximize the use of limited resources as the proportion of older adults (and the number of AD cases) continues to increase.

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Fratiglioni, L., Hemmy, L. S., Bäckman, L., Wahlund, L.-O., Wang, H., Livner, Å., Frank, A., & Lim, K. O. (July, 2006). *White matter integrity in aging – Relationship to vascular risk and cognition.* Presentation at the 10th International Conference on Alzheimer's Disease and Related Disorders, Madrid, Spain.

McCarten, J. R., Lewis, S. M., Leuthold, A. C., McPherson, S. E., Hemmy, L. S., Rottunda, S. A., Karageorgiou, E., & Georgopoulos, A. P. (July, 2006). *Classification of normal elderly, MCI, and mild AD using neuropsychological tests and self-reported memory function.* Presentation at the 10th International Conference on Alzheimer's Disease and Related Disorders, Madrid, Spain.

McCarten, J. R., Hemmy, L. S., McPherson, S. E., Dysken, M. W., & Lim, K. O. (July, 2006). *Computer-based diagnostic algorithm for dementia: Comparison to expert opinion.* Presentation at the 10th International Conference on Alzheimer's Disease and Related Disorders, Madrid, Spain.

McCarten, J. R., Hemmy, L. S., Rottunda, S. J., and Kuskowski, M. A. (March, 2005). *Age bias delays early recognition of AD in older adults.* Presentation at Molecular Mechanisms of Neurodegeneration: A Joint Biochemical Society/Neuroscience Ireland Meeting, Dublin, Ireland.